Initiation of Ventricular Extrasystoles by Myocardial Stretch in Chronically Dilated and Failing Canine Left Ventricle

Zifa Wang, MD; L. Katherine Taylor, MS; William D. Denney, MD; David E. Hansen, MD

Background Stretch-induced arrhythmias (SIAs) can be elicited in normal canine left ventricles by transient diastolic dilatation. Since clinically important ventricular arrhythmias arise most commonly in failing and dilated ventricles, we hypothesized that the arrhythmogenic effect of transient diastolic stretch would be enhanced in chronically failing canine hearts.

Methods and Results Heart failure was induced in seven dogs by right ventricular pacing at 250 min⁻¹ for 20.2±1.6 days. Left ventricular (LV) mechanical properties were measured in vivo with serial echocardiograms in these seven dogs with the dogs awake and tranquillized to confirm the development of LV dilatation and failure. By the third week of pacing, average short-axis area ejection fraction decreased by 64.3% (P<.001) as end-diastolic and end-systolic diameters increased by 25.9% and 50.7%, respectively (P<.001). After heart failure was established, the hearts were harvested and in vitro data were obtained as an isolated, blood-perfused ventricle preparation. A computerized servo pump system connected to an LV intracavitary balloon was used to measure and control LV volume. Results were compared with in vitro data obtained from eight ventricles not subjected to pacing (controls). LV contractility, quantitated in vitro as the slope of the peak isovolumic pressure-volume relation (Emax) normalized to LV cavity size, was much lower in the heart failure group than in controls (182±18 versus 365±38 mm Hg mL⁻¹, P<.001). In all isolated hearts, SIAs were induced using an electromechanical stimulation protocol in which eight paced beats at 2 Hz were followed by a transient increase in LV volume during early diastole. Prestretch volume (Vᵢ) was selected to yield end-diastolic pressures of 4 to 8 mm Hg in all hearts. The fractional increase in LV volume (∆V) that produced SIAs 50% of the time (ΔV₉₀/Vᵢ) was smaller in failing hearts than in controls (0.78±0.04 versus 1.18±0.17, P=.009), indicating an increased sensitivity to SIAs in the failing hearts. Although ventricular pairs were occasionally induced in both groups, the great majority of the arrhythmias induced in both groups were single extrasystoles, and nonsustained runs of ventricular tachycardia were never elicited in either group. LV end-diastolic and peak stretch pressures were similar in the two groups, but LV end-diastolic wall stress was higher by 35.7% (P=.029) in the dilated failing ventricles because LV hypertrophy, which tends to normalize wall stress as the heart dilates, did not occur during the 3 weeks of pacing. For stretch stimuli of comparable arrhythmogenic effectiveness, peak LV wall stress during stretch was similar in the two groups, whereas the fractional increase in volume was significantly smaller in the heart failure group, indicating impaired viscoelastic properties in the failing ventricles. In five control ventricles, acute exposure to 0.5 μmol/L dobutamine increased ventricular sensitivity to the induction of SIAs, as shown by a decrease in ∆V₉₀/Vᵢ from 1.27±0.16 to 1.06±0.11 (P=.04).

Conclusions Altered mechanical properties and/or neurohumoral adaptations associated with chronic dilation and failure predispose the ventricle to induction of ventricular extrasystoles by transient LV diastolic stretch. (Circulation. 1994;90:2022-2031.)

Key Words • heart failure • mechanics • arrhythmia • ventricles

Serious ventricular arrhythmias arise most commonly in failing and dilated ventricles and are a major cause of death in patients with severe congestive heart failure.1,2 Multiple factors such as electrolyte disturbances, myocardial injury and scarring, proarrhythmic effects of various pharmacological agents, and catecholamines may play important roles in arrhythmogenesis in such patients. In addition, mechano-electrical feedback, the process by which mechanical loading alters cardiac electrophysiology,3-4 may be another important mechanism for arrhythmia development in this setting.

Our laboratory has previously shown that transient diastolic stretch can induce arrhythmias in the normal canine heart.4 The purpose of this study was to test the hypothesis that the arrhythmogenic effect of transient diastolic stretch is enhanced in chronically dilated failing canine ventricles. We used chronic rapid ventricular pacing in the dog as a simple and dependable means of inducing heart failure.5 Hemodynamic and neurohumoral changes in tachycardia-induced heart failure are similar to those observed with biventricular cardiac dysfunction in humans.6,7 Evidence of myocardial dysfunction in patients with incessant tachyarrhythmias suggests that this model may be analogous to a human disease.8 We found that dilated failing hearts were more susceptible than control hearts to the arrhythmogenic effects of transient diastolic stretch and provide evidence that this might be due to altered mechanical properties or to neurohumoral adaptations associated with chronic severe heart failure. Thus, mechanoelec-
trical feedback effects, capable of inducing arrhythmias, may be important in the initiation of ventricular arrhythmias in dilated and chronically failing ventricles.

**Methods**

**Experimental Procedures**

All of these animal studies conform to the guiding principles of the American Physiological Society. Seventeen physically healthy, mongrel dogs were randomized to one of two groups. In one group (nine dogs), heart failure was induced by pacing tachycardia as described below. The results of in vitro studies in the heart failure group were compared with data obtained in the remaining eight dogs (controls). In the control group, heart failure was not induced.

**Heart Failure Model**

Nine adult mongrel dogs (average weight, 26.5 ± 4.0 kg) were anesthetized with sodium pentobarbital (30 mg/kg IV) and mechanically ventilated. A unipolar endocardial pacing electrode was advanced to the right ventricular apex under fluoroscopic guidance through the right internal jugular vein using sterile technique. The pacing lead was connected to a programmable pulse generator (model 8329, Medtronic, Inc.), which was implanted subcutaneously in the neck right laterally. The animals were allowed to recover for 1 day. The pacemaker was then programmed to a rate of 250 min⁻¹ until heart failure was well established. The pacing rate was briefly reduced to 120 min⁻¹ when weekly echocardiographic studies were performed for the purpose of confirming the progression to left ventricular (LV) dilation and failure. Heart failure animals were examined for evidence of heart failure and weighted daily. The hearts were harvested for in vitro studies as an isolated heart preparation when heart failure was well established, an average of 20.2 ± 1.6 days after pacing was initiated. The following echocardiographic and clinical criteria were used to determine the timing of the in vitro studies: a decrease in LV short-axis area ejection fraction ≥50% and/or the presence of clinical signs of heart failure (ascites, rales, tachypnea, or weight gain).

**Treatment of Control Animals**

The eight control animals (average weight, 24.6 ± 3.4 kg) did not undergo sham operations because it was not the purpose of this study to prove that incessant tachycardia results in cardiomyopathy. hearts from these healthy dogs were harvested for in vitro studies to provide control data from normal hearts. No echocardiographic studies were performed in the control group. Differences in LV size and function were confirmed by the in vitro studies.

**Echocardiographic Studies**

In the heart failure group, echocardiographic studies were performed just before the initiation of rapid right ventricular pacing and at 1-week intervals thereafter until heart failure was well established. Thirty minutes before echocardiographic studies, the dogs were tranquilized with chlorpromazine (1 mg/kg IM), and the pacemaker then was programmed for pacing at 120 min⁻¹. Two-dimensional short-axis echocardiographic images were obtained with a 5-MHz phased-array transducer (Hewlett Packard) at the level of the papillary muscle tips with the animal lying comfortably at rest in the left decubitus position. Technically excellent echocardiographic images were obtained in all animals. The pacing rate was increased to 250 min⁻¹ immediately after the echocardiographic studies were completed.

**Isolated Heart Preparation**

The isolated, perfused canine heart preparation has been previously described.9-10 Dogs were anesthetized with a combination of morphine (3 to 4 mg/kg IM) and α-chloralose (100 mg/kg IV). A median thoracotomy was performed under artificial ventilation, and the subclavian artery was cannulated and connected to the perfusion system. A fluid-filled cannula was inserted through the brachiocephalic artery into the proximal aorta and was connected to a pressure transducer (model 231D, Gould) to monitor coronary perfusion pressure. The right ventricle was vented at the apex and drained by gravity to a venous collection reservoir. The heart was then metabolically supported as it was surgically excised and connected to the servo-controlled ventricular loading system described below, with a compliant balloon placed within the LV cavity. A micromanometer-tipped catheter (model SPC-330A, Millar Instruments) positioned within the balloon allowed continuous measurement of instantaneous LV pressure. Pacing leads were attached at the LV apex, and plunge electrodes were inserted into the anterior ventricular wall to record bipolar ventricular electrogamms. A spring-loaded epicardial contact electrode was used to record the monophasic action potential (MAP) from the LV wall.11

**Coronary Perfusion System**

The heart was metabolically supported by a recirculating perfusate, which was diazylzed on a nonrecirculating dialyzer to maintain glucose and electrolyte homeostasis and to remove metabolic products. The dialysate was a physiologically buffered salt solution composed of (mmol/L) CaCl₂ 1.0, NaCl 110, KCl 5.0, MgCl₂ 1.2, NaH₂PO₄ 1.2, NaHCO₃ 26.0, and glucose 11. The perfusate was composed of this same solution to which 5% neonatal calf serum was added. Heparinized packed red blood cells prepared from bovine blood were filtered to remove leukocytes and platelets (model RC 100, Pall Biomedical Products). The bovine erythrocytes were then added to the perfusate to yield a leukocyte- and platelet-poor perfusate with a physiological hematocrit (35% to 40%). The perfusate was warmed to 37°C by a thermocirculator (model 50-1932, Harvard Apparatus) and was equilibrated with a gaseous mixture of 95% O₂ and 5% CO₂ by a hollow-fiber oxygenator (PLEXUS 2, Shiley, Inc). Coronary perfusion pressure was maintained at 80 mm Hg throughout the experiment by a computerized servo-regulated peristaltic pump.

**Ventricular Loading System**

The servo-regulated ventricular loading system consisted of a hydraulic piston (model C-MS4-PM, American Standard) driven by a linear motor (model VG 100-4, Vibration Test System). A resistive linear variable displacement transducer (LVDT, model SLE-S-50-1, Waters) sensed the position of the piston, its output having been calibrated to measure absolute volume (linearity ±0.1%). The output of the LVDT was digitized at 1000 Hz by a personal computer (486-33C EISA, ZEOS International) using a 12-bit analog-to-digital (A-to-D) converter (Labmaster TM-100, Scientific Solution). The computer continuously subtracted the actual digitized LV volume signal from the desired LV volume to determine the volume error, Vₑ, and an output signal (proportional) to Vₑ was sent by a digital-to-analog converter on the Labmaster TM-100 board to a 1000-W solid-state power amplifier (model 7560, Techron). The amplified Vₑ signal drove the linear motor to the desired volume.

**Experimental Protocol**

Standard hemodynamic parameters were measured with the ventricle beating in the isovolumic mode while paced at 2 Hz. Pacing was performed at twice diastolic threshold using an electronic circuit that produced an electrically isolated 2-millisecond square wave of constant current triggered by the computer. Data were collected as LV volume was varied in steps of 2 to 5 mL, such that end-diastolic pressure ranged between 0 and 30 mm Hg. To ensure a steady hemodynamic state, 2 minutes was allowed to elapse between changes. From these data, end-diastolic pressure-volume relationships (EDPVR)
Pressure-Volume Relations

Steady-state data obtained at multiple volumes were used to derive pressure-volume relations. All data were analyzed by computer using software developed in our laboratory. Diastolic pressure (at R wave), peak systolic pressure, and maximum rate of pressure rise (dP/dt\text{max}) were averaged from 10 steady-state beats at each volume. The plot of peak systolic pressure against cavity volume was fitted by linear regression to the time-varying elastance model of Suga et al.\textsuperscript{13,14}:

\[ P_{\text{max}} = E_{\text{max}} (V - V_0) \]

where \( P_{\text{max}} \) is the peak LV isovolumic pressure, \( V \) is LV cavity volume, \( V_0 \) is the volume-axis intercept, and \( E_{\text{max}} \) is the slope. Because the sizes of control and failing ventricles differed greatly, \( E_{\text{max}} \) was normalized to midwall volume at an end-diastolic pressure of 15 mm Hg.\textsuperscript{15-18} The LV midwall volumes (\( V_m \)) were calculated without assumptions regarding ventricular geometry using the following equation:

\[ V_m = \frac{(V_c^{1.3} + (V_c + V_v)^{1.3})^2}{2} \]

where \( V_c \) is LV cavity volume, and \( V_v \) is LV wall volume (calculated as LV mass divided by tissue density 1.055).

The relation between end-diastolic pressure and volume was analyzed by fitting pressure-volume pairs obtained over the physiological range to an exponential equation of the form

\[ P_{\text{ed}} = a \cdot e^{B V_{\text{ed}}} + C \]

where the fitting parameters, \( a \), \( B \), and \( C \), were determined by a standard nonlinear regression technique described previously. The end-diastolic hydraulic stiffness (\( E_d \)) was calculated at 15 mm Hg diastolic pressure from the following equation:

\[ E_d = V_{\text{ed}} \cdot \frac{\text{d}P_{\text{ed}}}{\text{d}V_{\text{ed}}} \]

where \( \text{d}P_{\text{ed}}/\text{d}V_{\text{ed}} \) was determined by differentiation of Equation 3, and \( V_m \) is the LV midwall volume calculated from Equation 2.

Ventricular Wall Stress

The LV wall stress was calculated by the following equation.\textsuperscript{18-20}

\[ \sigma = \frac{(3/2) \cdot P}{\ln[(V_c + V_v)/V_v]} \]

where \( \sigma \) is average wall stress, \( P \) is LV intracavitary pressure, \( V_c \) is cavity volume, and \( V_v \) is wall volume. End-diastolic wall stress was calculated for a LV cavity volume corresponding to \( V_c \). Peak wall stress at \( \Delta V_{\text{ed}} \) was calculated with peak pressure during the stretch (\( P_s \)) and the peak stretch volume (\( V_c + \Delta V_{\text{ed}} \)).

Analysis of MAP Tracings

The MAP duration at 20\%, 70\%, and 90\% repolarization was also determined from steady-state beats, as described in detail elsewhere.\textsuperscript{11} While stretch-induced depolarization (SID) of the ventricular myocardium was observed in all studies, no quantitative comparison of SIDs was performed because absolute changes in transmembrane potential cannot be determined using the MAP catheter technique.

Stretch-Induced Arrhythmias

The stretch response data were analyzed by a computerized method to detect QRS complexes and action potentials during the 2000-millisecond monitoring period of the reference and stretch sequences. To ensure that beats observed during the monitoring period were actually SIs and not early spontaneous escape beats, the time interval that excluded at least 95%
of the escape beats (t escape) was calculated using data collected during the reference sequences. The stretch sequences then were examined for QRS complexes and MAP signals during the monitoring period, and SIAs were defined as QRS complexes and action potentials that followed a stretch and arrose during the stretch period when there was at least 95% confidence that they were not ventricular escape complexes (ie, earlier than t escape or less than 500 milliseconds after the onset of stretch, whichever time interval was smaller). The probability of an SIA (P SIA) then was determined for each ΔV by dividing the number of SIAs by the total number of stretch sequences at that ΔV. A minimum of 20 stretch sequences was used in the determination of P SIA at each ΔV.

Because of the size difference between the control and failing ventricles, the amount of stretch was expressed as the fractional volume change, ΔV/VI, with VI being the initial volume (at P Ea = 6 mm Hg) from which the volume excursion departed. The relation between the intensity of the stress (ΔV/VI) and P SIA was fitted to a Boltzmann distribution using the equation

\[ P_{SIA} = C_b + \frac{A}{1 + e^{(\Delta V/V I - \Delta V_{50}/V I)}} \]

where A, K, and C b are fitting parameters, and ΔV_{50}/V I represents the fractional stretch resulting in P SIA of 0.5 (ie, SIA in 50% of tests). A nonlinear regression procedure was used to determine the fitting parameters. The convergence criterion for this iterative procedure was a change of less than 0.1% for all parameters.

**Statistical Considerations**

All data are presented as mean±SEM. Preliminary evaluation of our data using scatterplots indicated that the assumption of a normal distribution was invalid given the relatively small number of observations made (seven or eight ventricles in each group). Therefore, comparison of data obtained in control and failing ventricles was accomplished using nonparametric tests for two independent observations (Mann-Whitney U test) for all variables. Friedman's nonparametric two-way ANOVA was used to evaluate the repeated-measurements design of the echocardiographic and dobutamine studies. When Friedman's test revealed a significant treatment effect, Wilcoxon's nonparametric test for paired observations was used to determine which means differed. Differences with a value of P<.05 were accepted as statistically significant.

**Results**

Of nine dogs subjected to rapid pacing, one died suddenly during pacing and one died during induction of anesthesia. The seven remaining dogs make up the heart failure group. All dogs of this group developed clinical signs of congestive heart failure, including anorexia and lethargy. Two of these dogs had severe ascites and dyspnea and were treated with furosemide (10 mg IV).

**In Vivo Dimensions and Performance**

Echocardiographic data from the heart failure dogs are provided in Table 1. Short-axis area ejection fraction progressively decreased by 62.4% (P<.001) as end-diastolic and end-systolic diameters increased week by week, with overall increases of 25.3% and 33.5% (P<.001), respectively, by the third week. Although the LV chamber dilated, LV wall thickness did not change significantly. These data are similar to those previously reported, in which chronic rapid pacing was carried out in dogs, using a comparable pacing rate and duration.2,21

**In Vitro Mechanical Properties**

Representative peak systolic pressure-volume relations (ESPVR) and corresponding end-diastolic pressure-volume relations (EDPVR) from a normal and a failing heart are shown in Fig 1. The end-systolic pressure-volume points were well fitted by the linear regression line, and this example shows the characteristic reduction in the slope of the ESPVR. The average correlation coefficient was .99 in this study. Comparison of EDPVRs reveals a rightward shift such that for any
given end-diastolic pressure, the cavity volume is larger in the failing heart. Indices of ventricular contractile performance derived from these relations are summarized in Table 2. On the average, size-normalized Emax was 50% lower in the failing hearts than in the controls (P < .001). End-systolic volume at a common end-systolic pressure of 50 mm Hg, as calculated from the regression equations, was 51% higher in failing hearts than in control hearts (P = .02). These changes are consistent with reduced LV contractile strength. End-diastolic volume at a common end-diastolic pressure of 15 mm Hg was increased 26% in the failing left ventricles (P < .05). End-diastolic hydraulic chamber stiffness, calculated as the slope of the EDPV at a common end-diastolic pressure of 15 mm Hg, was similar compared with normal ventricles. Thus, the failing ventricles were dilated, but the passive diastolic properties did not change much. These changes were not directly reflected by any one particular modeling parameter of Equation 3, as the fitting parameters were not significantly different in the control and failing hearts.

Electrophysiological Effects of Heart Failure

Electrophysiological characteristics are shown in Table 3. MAP durations at 20%, 70%, and 90% repolarization were significantly longer in failing hearts than in controls (P < .05). These findings are consistent with prolongation of the plateau phase of the action potential in the heart failure group. The ARP did not change significantly in the two groups (P = NS). The standard escape time, measured as tS, tended to be longer in the failing ventricles than in controls, but the difference was not significant (P = .092).

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### Table 2. Comparison of Ventricular Mechanics in Terms of End-Systolic and End-Diastolic Pressure-Volume Relations in Eight Control and Seven Failing Ventricles

<table>
<thead>
<tr>
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<th>Control Heart</th>
<th>Failing Heart</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emax, mm Hg/mL</td>
<td>2.83±0.25</td>
<td>1.61±0.27</td>
<td>.001</td>
</tr>
<tr>
<td>Normalized Emax, mm Hg</td>
<td>366±38</td>
<td>183±18</td>
<td>.001</td>
</tr>
<tr>
<td>V0, mL</td>
<td>6.68±1.71</td>
<td>14.97±4.16</td>
<td>.456</td>
</tr>
<tr>
<td>Vdp1, mL</td>
<td>25.0±2.7</td>
<td>50.9±8.2</td>
<td>.018</td>
</tr>
<tr>
<td>a, mm Hg</td>
<td>2.74±0.76</td>
<td>2.3±1.02</td>
<td>.710</td>
</tr>
<tr>
<td>β, mL⁻¹</td>
<td>0.062±0.006</td>
<td>0.056±0.012</td>
<td>.097</td>
</tr>
<tr>
<td>C, mm Hg</td>
<td>−6.8±1.76</td>
<td>−3.82±1.47</td>
<td>.165</td>
</tr>
<tr>
<td>Vdp95, mL</td>
<td>37.08±1.27</td>
<td>50.12±5.47</td>
<td>.017</td>
</tr>
<tr>
<td>Edg, mm Hg</td>
<td>173±24</td>
<td>114±12</td>
<td>.052</td>
</tr>
</tbody>
</table>

Emax indicates slope of end-systolic pressure-volume relation (ESPVR); Normalized Emax, product of Emax, and left ventricular (LV) midwall diastolic pressure of 15 mm Hg; V0, volume axis intercept of ESPVR; Vdp1, calculated LV volume at a common end-systolic pressure of 50 mm Hg; a, β, and C, fitting parameters of end-diastolic pressure-volume relation (Equation 3, see text); Vdp95, calculated LV volume at end-diastolic pressure of 15 mm Hg; Edg, end-diastolic hydraulic stiffness at end-diastolic pressure of 15 mm Hg.

Data are mean±SEM. Probability values computed by Mann-Whitney’s nonparametric U test for unpaired samples.

### Table 3. Comparison of Cardiac Electrophysiology in Eight Control and Seven Failing Left Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Control Hearts</th>
<th>Failing Hearts</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARP, milliseconds</td>
<td>217±14.7</td>
<td>241±10.5</td>
<td>.231</td>
</tr>
<tr>
<td>tS, milliseconds</td>
<td>1565±143</td>
<td>1964±183</td>
<td>.092</td>
</tr>
<tr>
<td>MAPD20, milliseconds</td>
<td>158.5±6.6</td>
<td>184.9±7.5</td>
<td>.020</td>
</tr>
<tr>
<td>MAPD70, milliseconds</td>
<td>186.4±4.1</td>
<td>207.3±5.8</td>
<td>.014</td>
</tr>
<tr>
<td>MAPD90, milliseconds</td>
<td>198.6±5.5</td>
<td>235.7±15.7</td>
<td>.014</td>
</tr>
</tbody>
</table>

ARP indicates absolute refractory period; tS, time interval that excludes 95% of ventricular escapes; and MAPD20, MAPD70, and MAPD90, monophasic action potential duration at 20%, 70%, and 90% repolarization, respectively. Values are mean±SEM. Probability values computed by Mann-Whitney’s nonparametric U test for unpaired samples.

### Stretch-Induced Arrhythmias

Representative reference and stretch sequences of an SIA stimulation protocol are displayed in Fig 2. In the reference sequence, LV volume is held constant, while the MAP signal and LV pressure are monitored after an eight-beat pacing train (priming period). In the stretch sequence, a transient increase in diastolic volume of 16 mL delivered at 400 milliseconds after the final priming stimulus results in a small SID that coincides with the time of stretch and the early appearance of an SIA. In this example, a single ventricular extrasystole is induced by stretch. Ventricular pairs and occasional nonsus-

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![Fig 2. Protocol for initiating stretch-induced arrhythmias. Continuous recording of an entire reference sequence and stretch sequence are shown, beginning with the reference sequence. The upper tracing (Pacer) shows the timing of the eight-beat pacing trains, which were delivered at a cycle length of 800 milliseconds during the priming periods that preceded test periods (No Stretch and Stretch). In the reference sequence, there are no escape beats during the unpaced observation period as left ventricular volume (LVV) is held constant at 20 mL (bottom tracing). In the stretch sequence that immediately followed, a transient 16-mL (ΔV/L =0.8) increase in LVV (bottom tracing) was delivered 400 milliseconds after the last pacing stimulus. This stretch stimulus resulted in an early stretch-induced arrhythmia (SIA) arising approximately 200 milliseconds after the onset of the stretch in the form of a single ventricular ectopic beat. MAP indicates monophasic action potential; LVP, left ventricular pressure; and SID, stretch-induced depolarization.](http://circ.ahajournals.org/content/90/4/1026/F2)
Fig 3. Modeling of the relation between stretch stimulus characteristics and the probability of eliciting an arrhythmia in a single failing left ventricle. The probability of eliciting a stretch-induced arrhythmia (P_{SIA}) is plotted vs stretch volume (ΔV, top scale) and ΔV/Vi (bottom scale), the stretch volume normalized to initial volume (Vi). Vi was 30 mL, yielding a left ventricular end-diastolic pressure of ≈6 mm Hg. Solid curve represents the best fit of data using logistic regression techniques.

Fig 5. Plots show distributions of ΔV_{50}/V_{i} according to prestretch end-diastolic pressure (P_{i}) and peak stretch pressure (P_{p}). In the range of pressures studied, there was no relation between pressure and the stretch fraction, resulting in P_{SIA} of 0.5 (ΔV_{50}/V_{i}). Plots are presented to show that initial and peak pressures were comparable in the two groups; mean ΔV_{50}/V_{i} was lower in failing hearts than in controls (P= .009 by Mann-Whitney U test).

Pressures and Stresses During Stretch

To determine whether the mechanical characteristics of the stretch stimulus differed between the failing and control ventricles, the peak pressure and peak average LV stress during the stretch were computed. Fig 5 shows ΔV_{50}/V_{i} values for each experiment plotted against the end-diastolic pressures at V_{i} and against the corresponding peak stretch pressures (P_{p}). The latter were calculated from plots of P_{SIA} versus P_{p}, using logistic regression techniques to determine the value of P_{p}, resulting in a P_{SIA} of 0.50, as illustrated in Fig 3. It is seen that the diastolic pressures at V_{i} of controls and failing hearts were in a comparable range, as per experimental design. Also, the peak stretch pressures of controls and failing hearts were in a comparable range, this being an uncontrolled variable. The stretch fractions yielding a P_{SIA} of 0.5 (ΔV_{50}/V_{i}) were generally lower (P= .009) in the failing hearts than in controls.

Table 4 shows the ventricular mass and calculated wall stress for the control and failure groups. Despite the increased LV chamber volume in the failing hearts, there was no significant difference between control and failing ventricles with respect to LV mass or the ratio of LV mass to body weight. The end-diastolic pressure at prestretch volume (P_{i}) and peak stretch pressure (P_{p}) were similar in the two groups (P=NS). The average midwall stress (σ_{m}) associated with P_{i} was higher in failing chambers than in controls because the pressures and wall mass were similar, but cavity volumes were higher in failing ventricles. Peak stress during the ΔV_{50} volume pulse (σ_{p}) also tended to be higher in the heart failure group, but this difference did not reach the level of significance (P=.27). Thus, the mechanical characteristics of the stretch stimulus required to elicit SIAs 50% of the time were similar in the control and failure groups when evaluated in terms of the peak LV pressure or wall stress.

To evaluate more fully the mechanical characteristics of the stretch stimulus in both groups, we plotted the relation between the fractional increase in LV volume (ΔV/V_{i}) and the peak LV wall stress attained during the stretch (σ_{p}). This relation, which reflects viscoelastic
Table 4. Determinants of LV Wall Stress and Characteristics of Stretch Stimulus in Eight Control and Seven Failing Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Control Hearts</th>
<th>Failing Hearts</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M LV, g</td>
<td>195.7±10.9</td>
<td>197.7±18.2</td>
<td>.536</td>
</tr>
<tr>
<td>M LV/M body, g/kg</td>
<td>7.7±0.4</td>
<td>7.4±0.3</td>
<td>.541</td>
</tr>
<tr>
<td>V i, mL</td>
<td>19.1±0.6</td>
<td>32.6±2.6</td>
<td>.001</td>
</tr>
<tr>
<td>P, mm Hg</td>
<td>6.10±0.46</td>
<td>6.41±0.51</td>
<td>.694</td>
</tr>
<tr>
<td>P p at ΔV 50, mm Hg</td>
<td>68.4±7.7</td>
<td>68.1±7.5</td>
<td>.779</td>
</tr>
<tr>
<td>σ v, g/cm²</td>
<td>3.73±0.21</td>
<td>5.06±0.43</td>
<td>.029</td>
</tr>
<tr>
<td>σ p at ΔV/V i=1.0, g/cm²</td>
<td>57.0±17.8</td>
<td>115.1±29.5</td>
<td>.001</td>
</tr>
<tr>
<td>σ p at ΔV 50, g/cm²</td>
<td>58.8±7.2</td>
<td>71.9±9.0</td>
<td>.397</td>
</tr>
</tbody>
</table>

MLV indicates left ventricular (LV) mass; M body, dog body weight; V i, prestretch volume; P i, end-diastolic pressure at V i; P p at ΔV 50, peak pressure during diastolic stretch with ΔV = ΔV 50 (i.e., at V i+ΔV 50); σ v, LV wall stress at end-diastolic pressure P i; σ p at ΔV/V i=1.0, peak LV wall stress during diastolic stretch with fractional volume increase=1.0; and σ p at ΔV 50, peak LV wall stress during diastolic stretch with ΔV = ΔV 50.

Data are mean±SEM. Probability values computed by Mann-Whitney's nonparametric U test for unpaired samples.

The properties of the ventricle, was highly linear in all ventricles, with mean correlation coefficients of .980±.021. The slope of the σ p/ΔV/V i relation was steeper in the heart failure group than in controls (159±44 versus 84±39 g/cm², P = .0037), whereas the ΔV/V i axis intercept was similar (0.27±0.12 versus 0.18±0.47, P = .694). The mean value of σ p with ΔV/V i=1.0 was higher in the heart failure group (115±29 versus 57±18, P = .006). These findings are consistent with impaired viscoelastic properties in the heart failure group.

The Effects of β-Adrenergic Stimulation With Dobutamine on Stretch-Induced Arrhythmias

As shown in Table 5, 0.5 μmol/L dobutamine produced significant increases in peak LV isovolumic pressure generation (P p) and dP/dt max, as one would expect with this positive inotropic agent. For these experiments, a uniform prestretch volume (V i) of 20 mL was used, resulting in a somewhat lower end-diastolic pressure during the dobutamine studies. Since our interpretation of the dobutamine data is based on comparison of repeated observations in each ventricle, the low level of end-diastolic pressure should not influence our conclusions regarding the effects of dobutamine the inducibility of SIs. This was associated with an enhanced ability to produce SIs, as indicated by significant decreases in the mean value of ΔV 50 and ΔV 50/V i compared with baseline. Dobutamine also slightly reduced MAP durations and t 90 (P <.05).

Discussion

Patch clamp studies have demonstrated that stretch-activated ion channels (SAC) exist in cardiomyocytes. In our earlier studies, we found that transient end-diastolic stretch of isolated canine left ventricles harvested from healthy dogs can induce arrhythmias. These SIs can be blocked by Gd3+, a potent stretch-activated channel blocker. Thus, SACs may play an important role in the process of mechanotransduction signaling in the nondiseased hearts, but one cannot be certain that this function would persist in the setting of chronic severe heart failure. The present study was undertaken to test the hypothesis that the arrhythmogenic effect of transient diastolic stretch would be not only demonstrable but enhanced in the chronically dilated failing ventricle. The results support this hypothesis.

Characteristics of Failing Heart Model

Many studies have demonstrated that chronic rapid ventricular pacing in dogs can induce congestive heart failure characterized by ventricular dilation, elevated cardiac filling pressures, and decreased fractional shortening. Riegger and Liebau confirmed that pacing

Table 5. Response to Acute β-Adrenergic Stimulation With Dobutamine in Five Control Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobutamine</th>
<th>Washout</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔV 50, mL</td>
<td>25.4±3.2</td>
<td>21.2±2.3*</td>
<td>22.5±2.4</td>
<td>.041</td>
</tr>
<tr>
<td>ΔV 50/V i</td>
<td>1.27±0.16</td>
<td>1.06±0.11*</td>
<td>1.12±0.12</td>
<td>.041</td>
</tr>
<tr>
<td>P i, mm Hg</td>
<td>0.7±0.5</td>
<td>0.1±0.4*</td>
<td>−0.4±0.4</td>
<td>.022</td>
</tr>
<tr>
<td>P p at V i, mm Hg</td>
<td>31.5±6.6</td>
<td>44.7±8.4*</td>
<td>24.6±5.1</td>
<td>.007</td>
</tr>
<tr>
<td>dP/dt max</td>
<td>328.8±99.6</td>
<td>501.2±143.1</td>
<td>271.6±77.5</td>
<td>.015</td>
</tr>
<tr>
<td>ARP, milliseconds</td>
<td>190.6±5.3</td>
<td>177.6±7.1</td>
<td>195.4±19.6</td>
<td>.247</td>
</tr>
<tr>
<td>t 90, milliseconds</td>
<td>1492±225</td>
<td>1134±260†</td>
<td>1639±281</td>
<td>.022</td>
</tr>
<tr>
<td>MAPD 50, milliseconds</td>
<td>143.7±11.3</td>
<td>126±10.3</td>
<td>143.2±15.4</td>
<td>.050</td>
</tr>
<tr>
<td>MAPD 70, milliseconds</td>
<td>184.3±8.2</td>
<td>163.5±8.6</td>
<td>178.8±13.5</td>
<td>.068</td>
</tr>
<tr>
<td>MAPD 90, milliseconds</td>
<td>200±10.9</td>
<td>183.4±9.8*</td>
<td>196±12</td>
<td>.074</td>
</tr>
</tbody>
</table>

ΔV 50/V i is fractional stretch at ΔV 50; P i, end-diastolic pressure at V i; P p at V i, peak pressure at V i; ARP, absolute refractory period; t 90, time interval that excludes 95% of ventricular escapes; and MAPD 50, MAPD 70, and MAPD 90, monophasic action potential at 20%, 70%, and 90% repolarization, respectively.

Data are mean±SEM. Probability values were determined by Friedman's nonparametric test for multiple related samples design.

*P <.05 vs baseline by Wilcoxon's nonparametric test for two related samples.
†P <.05 vs baseline and washout by Wilcoxon's nonparametric test for two related samples.
dogs for 2 weeks at 240 to 280 min\(^{-1}\) increased pulmonary wedge pressure and reduced cardiac output. Plasma renin activity, angiotensin II, aldosterone, vasopressin, norepinephrine, and epinephrine levels were also elevated,\(^7,27\) as is frequently noted in patients with heart failure.\(^{12,28}\) Similar studies by Wilson et al\(^5\) indicate that the hemodynamic dysfunction resembles biventricular heart failure in humans. This impaired cardiac function was characterized by left and right ventricular dilation without significant change in LV wall thickness. Histological examination by one group\(^6\) revealed no evidence of infarction, myofiber hypertrophy, or fibrosis. Another group\(^25\) observed interstitial edema, vascular congestion, and focal necrosis with eosinophilic myocytes in the paced animals. Our experience with this model was similar to that of other investigators. Ventricular contractility was significantly decreased in the failing heart, as judged from normalized E\(_{\text{max}}\). The use of normalized E\(_{\text{max}}\) to compare the contractile state of ventricles from these two groups compensates for the tendency for the slope of the ESPVR to decrease with increasing ventricular size.\(^15-17\)

Despite overall dilation of the LV chamber and a clear rightward shift of EDVPR, the increase of V\(_{\text{p}}\) was not significant, as also observed by Wolff et al.\(^21\) Although ventricular dimensions increased significantly, ventricular mass did not increase sufficiently to normalize ventricular wall stress; thus, the LV end-diastolic ventricular wall stress was elevated in the heart failure group despite similar end-diastolic pressures in the two groups. Likewise, peak LV wall stress during the volume pulse tended to be higher in the dilated failing hearts, although this difference did not reach the level required for statistical significance.

Interestingly, we found that APD measured at 20%, 70%, and 90% repolarization was significantly greater in failing ventricles than in controls; other indices of electrical interval duration, such as ARP and t\(_{95}\), tended to be greater in the failing hearts, but this was not significant. Thus, the increased sensitivity to the arrhythmogenic effects of stretch in the failure group cannot be explained in terms of electrical refractoriness. The prolongation of the MAP may reflect (1) Na\(^+\) channel inactivation, (2) alterations in the Na\(^+\)-Ca\(^{2+}\) exchange current, (3) prolongation of the slow inward Ca\(^{2+}\) current, or (4) delay of repolarizing K\(^+\) currents. Thus, the determinants of MAP duration are quite complex, and it is not possible to determine the precise mechanism for prolongation of the MAP in our failing ventricles.

**Stretch-Induced Arrhythmias in the Failing Heart Model**

SIAs were produced by transiently increasing the volume of an LV intracavitary balloon during diastole in both control and failing ventricles. It was our intention to test the control ventricles and the enlarged failing ventricles under comparable conditions of stretch and overall load. With information available at the time of experiment, our best means of achieving comparable conditions was to set the initial volume (V\(_i\)) at the value resulting in a limited range of diastolic pressures. We chose modest initial pressures (4 to 8 mm Hg) so that the pulse volumes would not overstretch the muscle. Since the failing ventricle dilated without hypertrophy and the V\(_i\) of failing chambers was greater than that of controls, the wall stress at V\(_i\) (\(\sigma_i\)) was higher in the failing hearts than in controls (Table 4). Because failing ventricles were more susceptible to SIAs than controls (ie, smaller fractional increases in LV volume were required to elicit arrhythmias), the peak stress (\(\sigma_p\)) during stretches of comparable effectiveness (\(\Delta V_{\text{so}}\)) was similar in the two groups (Table 4). Our analysis of stress-strain (\(\sigma_p\Delta V/V\)) relations revealed a significantly higher slope in the failing ventricles such that peak LV wall stress during the stretch was higher in the chronically dilated and failing ventricles for comparable levels of stretch. For example, when \(\Delta V/V\) was 1.0, the peak LV midwall stress during the stretch was twice greater in the heart failure group than in controls (Table 4). Thus, the fact that \(\Delta V_{\text{so}}/V\) was smaller in the failing ventricles may be explained at least in part in terms of impaired viscoelastic properties in the heart failure group.

**Potential Mechanisms of Enhanced Ventricular Susceptibility to Stretch-Induced Arrhythmias in Heart Failure**

The principal new finding of this study is that the dilated failing ventricle is more prone to develop SIA than normal (Fig 4). In addition to the potential role of impaired viscoelastic properties (see above), several other mechanisms deserve consideration. Since gadolinium-sensitive SACs have been implicated in the genesis of SIAs, an alternative explanation is that the activity of SACs is increased in the dilated failing ventricle. Up-regulation of SACs could occur by either an increase in channel density or enhanced function of existing SACs. It is well known that ion channel function can be modulated by cAMP-dependent protein kinases that phosphorylate the channel.\(^29,30\) For instance, phosphorylation of consensus sites on the Ca\(^{2+}\) channel is known to increase Ca\(^{2+}\) permeability in cardiomyocytes.\(^31\) In the heart failure model that we used, chronic elevation of circulating catecholamines could mediate such cAMP-dependent changes. Indeed, we found that \(\beta\)-adrenergic stimulation potentiated the induction of arrhythmias in nonfailing control hearts (Table 5). Thus, our data support the notion that neurohumoral adaptations are likely to contribute to the enhanced ventricular sensitivity of SIAs, but we cannot be certain that these effects directly or indirectly involve SACs because cAMP modulates a number of important cellular processes in cardiac muscle.\(^32\) SIAs would be more likely to occur if the resting membrane potential was depolarized in the heart failure group. If the dilated failing hearts were partially depolarized at the time the stretch stimulus was delivered, then smaller SIDs would be capable of reaching threshold potential and initiating a propagated action potential. Since it has long been known that increases in diastolic fiber length or tension partially depolarize ventricular myocardium,\(^33\) the differences in SIA inducibility that we observed could be related to the higher LV end-diastolic wall stress observed in the failing ventricles (Table 4). Reductions in the Na\(^+\)-K\(^+\)-ATPase \(\alpha\)-subunit have been reported recently in the failing myocardium of dogs subjected to pacing tachycardia,\(^34\) which might also lead to a partially depolarized resting transmembrane potential. Unfortu-
nately, the MAP contact electrode does not provide absolute measurements of transmembrane potential; therefore, we cannot know whether such differences in resting transmembrane potential were present.

Identifying the mechanism of enhanced sensitivity to the arrhythmogenic effects of the transient diastolic stretch in the failing ventricles will require additional studies at the cellular and subcellular levels. The existence of SACs has been proven phenomenologically, but unfortunately, such channels have not yet been isolated and characterized at the molecular level. While microelectrode patch clamp recordings would be helpful, obtaining such data from mature myocytes has proven to be a difficult task.

SIAs most frequently are single ventricular extrasystoles, although pairs and nonsustained runs of ventricular tachycardia (VT) have been observed in our previous studies.10 In the present study, we were unable to induce VT in either group, and ventricular pairs were produced on less than 2% of the stretches in both the heart failure group and controls. This failure to induce VT in the heart failure group is one limitation of this particular heart failure model.

In patients with nonischemic dilated cardiomyopathy, sustained monomorphic VT is rarely induced using aggressive protocols unless there is a history of spontaneous arrhythmias of this type.3,5 Since sustained monomorphic VT can be induced by programmed electrical stimulation in the subset of patients with nonischemic dilated cardiomyopathy who presented with such arrhythmias, VT is considered to be a reentrant arrhythmia in the vast majority of such patients.25 Ventricular reentry is dependent on the presence of myocardial scarring,36 which is not a prominent feature of this heart failure model according to published studies of the pathology.5,25 Thus, it is not surprising that we did not induce VT in this model of heart failure with either the single programmed electrical stimulus or the mechanical stimulus. When ventricular pairs or runs occur in our isolated canine model, they probably represent triggered activity, since delayed afterdepolarizations are often present when repetitive firing of ventricular beats is elicited.10 Because the stretch stimulus used in this study is shorter than a single cardiac cycle, the focus of the investigation was on the genesis of the single extrasystole by stretch, but we can also conclude that there is nothing inherent in this model of heart failure that predisposes the hearts to the subsequent repetitive firing of ventricular beats by a mechanism of ventricular reentry or triggered activity. As such, the clinical relevance of these findings remains to be established, but one can imagine that extrasystoles triggered by a mechanism of transient diastolic stretch might initiate sustained VT in heart failure patients with the appropriate substrate, scarred myocardium.

Another limitation of this in vitro model is the lack of neurohumoral input to the heart, which might be particularly important in heart failure.12 To address this limitation, we tested the influence of $\beta$-adrenergic stimulation with dobutamine on the inducibility of SIAs in our model. These studies indicate that SIAs were more readily inducible when the heart was stimulated by the acute administration of this $\beta$-adrenoceptor agonist (Table 5). Based on these results, it is likely that the neurohumoral adaptations associated with chronic severe heart failure would probably potentiate the arrhythmogenic effect of transient diastolic stretch. The acute exposure of normal control hearts to dobutamine is an imperfect model of the effects of chronic exposure of failed hearts to circulating catecholamines because other important vasoactive agents (eg, angiotensin II or vasopressin) are also elevated in chronic severe heart failure. Moreover, we cannot be certain that the effects produced by catecholamines in our heart failure group did not reverse during the time course of our in vitro studies. Nevertheless, based on our results with acute administration of dobutamine, it would appear that the increased susceptibility for SIAs in chronically dilated failing ventricles may be mediated at least in part by high levels of circulating catecholamines.

Summary

Studies of SIAs were undertaken in a well-established dilated failing heart model. The reduction of systolic performance was shown to be a consequence of depressed myocardial contractility. We found that the chronically dilated failing ventricle is more sensitive to the induction of ventricular extrasystoles by a mechanism of transient diastolic dilatation than control ventricles, whereas the likelihood of inducing ventricular pairs was similar in the two groups, and ventricular tachycardia was not produced in ventricles of either group. The possible roles of altered myocardial mechanisms and the neurohumoral adaptations associated with heart failure in mediating this increased inducibility of ventricular extrasystoles were discussed. Additional studies in heart failure models where myocardial scarring is a prominent feature are required to better explain why serious ventricular arrhythmias arise most commonly in patients with dilated failing heart.37-41

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